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REVIEW ARTICLE

Efficacy of antimicrobial lock solutions in preventing catheter-related blood stream infection in haemodialysis patients: a systematic review and meta-analysis of prospective randomised controlled trials

Ahmad Maifada Yakasai[a]*, Hamza Muhammad[bc], Garba Iliyasu[bc], Aisha Muhammad Nalado[cd], Mahmood Muhammad Dalhat[bc], Zaiyad Garba Habib[e], Farouk Daiyabu[bc], Chinagozi Precious Edwin[f], Musa Baba Maiyaki[cg] and Daiyabu Alhaji Ibrahim[cg]

[a]*Infectious and Tropical Diseases Unit, Department of Medicine, Public Health and Diagnostic Institute, College of Medical Sciences, Northwest University, Kano, Nigeria*
[b]*Infectious and Tropical Diseases Unit, Department of Medicine, Bayero University, Kano, Nigeria*
[c]*Aminu Kano Teaching Hospital, Kano, Nigeria*
[d]*Nephrology and Haemodialysis Unit, Department of Medicine, Bayero University, Kano, Nigeria*
[e]*Department of Medicine, University of Abuja Teaching Hospital, Abuja, Nigeria*
[f]*Department of Microbiology, Aminu Kano Teaching Hospital, Kano, Nigeria*
[g]*Department of Medicine, Bayero University, Kano, Nigeria*
**Corresponding author, email: ahmadmaifada@gmail.com*

Background: Catheter-related blood stream infection (CRBSI) contributes to morbidity and mortality among patients on haemodialysis (HD). We carried out a systematic review and meta-analysis to assess the efficacy of antimicrobial lock solutions (ALS) in preventing CRBSI. Method: Electronic search of randomised controlled trials (RCTs) comparing ALS with other agents was performed up to January 2013. DerSimonian and Laird meta-analysis was performed to obtain pooled relative risk (RR) from which efficacy of ALS and numbers needed to treat (NNT) were calculated. In a restricted analysis, pooled RRs where compared using a test of interaction to calculate ratio of relative risks (RRR). Meta-regression analysis was employed to explore sources of heterogeneity. Results: Sixteen RCTs involving 2016 individuals met the inclusion criteria. The efficacy of ALS in preventing CRBSI was 80% with NNT of 3 patients to prevent one CRBSI. The RR of CRBSI was significantly lower with ALS compared with heparin-only lock solution [RR {95% confidence interval (CI)} = 0.20 (0.13-0.31)]. With low dose (≤ 5 mg/ml) and high dose (40 mg/ml) gentamicin-containing ALS, the RR (95% CI) of developing CRBSI was 0.03 (0.01-0.13) and 0.18 (0.03-0.98), respectively, with no significant difference [RRR (95% CI) = 0.2 (0.02-1.61), $p = 0.126$]. Heterogeneity was explained by a statistically significant association between rate of CRBSI and catheter days ($p = 0.037$). Conclusion: ALS are effective in preventing CRBSI. Low dose gentamicin should be preferred over high dose gentamicin as an ALS because it offers similar benefit in preventing CRBSI with lesser risk of toxicity from systemic leakage and subsequent development of drug resistance.

Keywords: antimicrobials, blood stream infection, catheter, efficacy, haemodialysis, meta-analysis, systematic review

Introduction

Long-term renal replacement therapy in the form of haemodialysis (HD) is challenged by the prevention of catheter-related infections mainly involving the blood stream, exit-site and tunnel. Catheters are commonly used among patients on HD when permanent vascular access has not been secured or is not ripe for dialysis. It has been reported that about 25% of all patients on HD have catheters and, at commencement of HD, up to 80% of patients required catheters.[1] The risk of catheter-related bloodstream infection (CRBSI) is high among catheter-dependent HD patients. Serious life-threatening complications of CRBSI, such as infective endocarditis, may require several days of hospital admission and generate an increased financial burden on chronic HD patients. The morbidity and mortality in this group of patients is worsened by catheter-related infections.[2]

Factors associated with the host, catheter, microorganism and dialysis interact to predispose catheter-dependent patients to the risk of developing CRBSI.[3,4] Bacteria that colonise catheters are usually located within a protective polysaccharide secretion commonly called a biofilm matrix, which has to be eradicated in order to prevent CRBSI. Guidelines on prevention of CRBSI initially emphasised on aseptic technique of catheter insertion, exit site dressing, catheter maintenance and prompt removal of the catheter when needed.[5] However, with better understanding of the concept of biofilms, antimicrobial lock solutions (ALS) were used in the prevention of CRBSI.[6] Antibiotics commonly used as ALS include gentamicin, amikacin, ciprofloxacin, cefotaxime, ceftazidime, cefazolin, minocycline and vancomycin.[7] Non-antibiotic agents with good antimicrobial properties are also used in ALS and include antiseptics, such as alcohol, citrate and taurolidine.[7] ALS are formed by putting these agents into the catheter lumen together with an anticoagulant, such as heparin.[7] Various studies have reported on the potential of ALS in preventing CRBSI,[8–14] as well as prolonging the time of onset of the first episode of CRBSI.[15] However there has been conflicting reports on the efficacy and potential risk of toxicity associated with the use of these agents among HD patients. We conducted this systematic review and meta-analysis of prospective randomised controlled trials (RCTs) to obtain pooled estimates of efficacy of ALS in preventing CRBSI.

Methods

Data bases search

Both electronic and manual search of relevant publications were conducted up to January 2013. Medline, Google Scholar, Excerpta Medical dataBASE (EMBASE), Web of Science, Cochrane data base, African Journals Online (AJOL), systematic reviews, infectious disease journals, nephrology journals and other websites were searched for English language publications on CRBSI in HD patients. Medical sub-heading (MeSH) terms used in different combinations in the search included:

- 'Catheter-related infection',
- 'Catheter-associated infection',
- 'Bacteraemia',
- 'Septicaemia',
- 'Blood stream infection',
- 'Line-associated infection,'
- 'Intravascular catheter',
- 'Antimicrobial lock',
- 'Antibiotic lock',
- 'Randomised controlled trial',
- 'Clinical trial', and
- 'Haemodialysis'.

Also manual search of references of all relevant studies and reviews was performed.

Inclusion and exclusion criteria

Studies included satisfied the following criteria:

(1) All were RCTs;
(2) Involved only adults 18 years and above;
(3) Used intraluminal ALS either alone or in combination with an anticoagulant for the prevention of CRBSI;
(4) Provided relative risk (RR) of CRBSI in both treatment and control groups, or had provided enough data to derive the RR; and,
(5) Reported incidence of CRBSI per 1000 catheter days.

Studies were excluded if they did not satisfy the inclusion criteria. Three reviewers independently assessed each study for eligibility. A fourth reviewer resolved disagreement between the reviewers when encountered.

Data extraction

Data was obtained using a standardised form. The information extracted included name of author, country, year of publication, demographic characteristics, study design, clinical and laboratory characteristics, type of catheter, ALS used, care of catheter exit site, catheter days, incidence of CRBSI and number of infections reported in each group.

Statistical analysis

RR with 95% confidence interval (CI) was computed for each trial. RR was defined as the risk of CRBSI in the treatment group divided by the risk of CRBSI in the control group. The log RR and the standard error of the log RR were computed for each trial. Also the logarithm of the incidence of CRBSI was computed for all the comparison groups. When no event was reported in one of the groups we added 0.5 to both the numerator and denominator of both groups before calculating the RR.[16] DerSimonian and Laird meta-analysis using random effect model (REM) or fixed effect model (FEM) was done on the RR and incidence estimates to obtain pooled results. The efficacy of ALS was determined by subtracting the risk difference from 1, whereas the number needed to treat (NNT) was calculated as the reciprocal of the risk difference.[17] In a restricted analysis, different RRs were compared using test of interaction to determine ratio of relative risk (RRR), 95% CI and *p*-value.[18] We examined publication bias using Begg's test, while small study effect was analysed using Egger's test.[19,20] Due to the inconsistency associated with these tests, publication bias was assumed present only if all the *p*-values in Begg's and Egger's tests were significant.[21,22] Sensitivity analysis was done to investigate the influence of single trial on pooled estimate.[23] Heterogeneity was assessed with I-squared statistics ($I^2 > 50\%$ indicates substantial heterogeneity). Study-level parameters associated with risk of CRBSI were explored via univariable, weighted, least squares meta-regression analysis. The Grading of Recommendations Assessment Development and Evaluation (GRADE) approach was used to assess the quality of included studies and the quality of clinical evidence.[24,25] Quality is down-graded if the study design is not a RCT, and if there are study limitations, inconsistency (substantial heterogeneity), imprecision, indirectness or publication bias. Imprecision is suggested by small sample size or wide/overlapping CI.[25] Where no justification for sample size was provided, we considered sample size adequate if at least 100 subjects were analysed.[26] Quality is up-graded where there is an exposure-response gradient, large effect size (ES) and no plausible confounding.[25] Appropriate formula was used to compute the ESs and were classified according to Cohen's method of small ES (up to 0.49), moderate ES (0.5 – 0.79) and large ES (≥0.8).[27] Data analysis was performed with Stata version 12.0 and GRADEprofiler version 3.6.1.

Results

Description of included trials

Sixteen RCTs satisfied the inclusion criteria,[8–11,14,15,28–36] and one of them had an additional sub-study[10] making a total of 17 studies that were analysed (Figure 1). The trials were reported between 2002 and 2012 and involved 2016 individuals across 9 countries. Four studies were done in the United States of America (USA), 3 in Saudi Arabia, 2 in Iran and one study each from England, Brazil, Netherlands, United Kingdom (UK), Canada, Korea and Australia. Other details are given in Table 1.

Quality assessment of included trials

Adequate concealment allocation was reported in seven[8,9,12,14,15,35,36] trials while six trials were double-blinded.[8,12,14,15,35,36] Analysis by intention-to-treat (ITT) was performed in 10 trials.[8,9,11,14,15,29–31,33–35] All included trials were randomised and had reported measures to curtail bias. Other parameters assessed were sample size, loss to follow-up, missing data management, confounders and baseline characteristics. According to the GRADE approach, two[14,34] of the studies were of high quality, thirteen[8–12,15,28,30–33,35,36] studies were of moderate quality and two[11,29] had low quality as shown in Table 2.

Characteristics of participants in the included trials

The trials involved 2016 adults on HD with a follow-up period of 6 to 12 months. The mean catheter days for trials reported from 2002 to 2007 and 2010 to 2012 was 5293 and 15369 days, respectively [mean difference (95% CI) = 10076 (2349 to 17803), $p = 0.01$]. The mean age of participants reported in 14 trials ranged from 48.3 to 66.3 years and 44.7 to 62.8 years for the

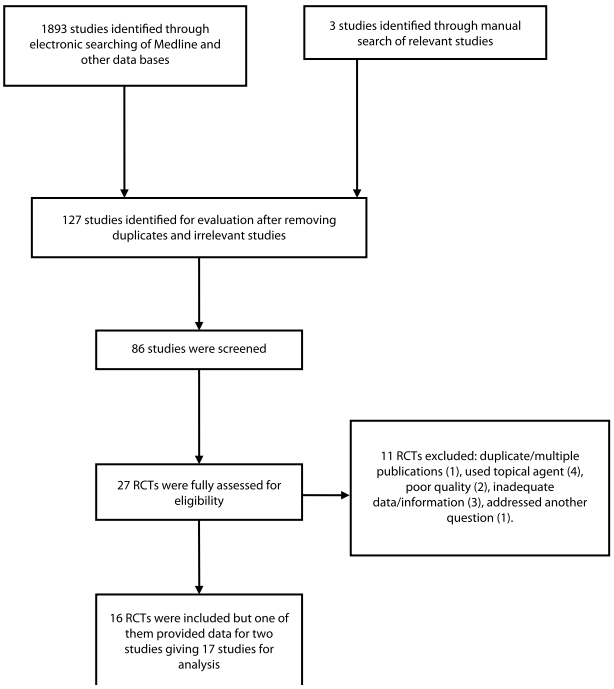

Figure 1: Flowchart of studies selection.

treatment and control groups, respectively. The proportion of female participants reported in 12 trials was 28% to 74% for the treatment group and 39.6% to 60% for the control group. The range of mean packed cell volume (PCV) reported in 8 trials was 26.4% to 33.5% for the treatment group and 27% to 34.5% for the control group.

The concentration of gentamicin used in the trials ranged from 0.32 mg/ml to 40 mg/ml. One of the trials that used 40 mg/ml of gentamicin reported median predialysis levels of 2.8 mg/ml with a range of 0.6 to 3.5 mg/ml among 42 patients randomised to gentamicin.[8] Symptoms of ototoxicity were reported in 4 of these 42 patients on high dose intraluminal gentamicin. However, with low dose gentamicin (5 mg/ml), McIntyre et al. reported that all random gentamicin levels were < 0.2 mg/ml and no patient complained of toxicity symptoms, though long term toxicity to such low levels could not be ruled out.[9] In another trial, Al-Hweish et al. reported that 40 mg/ml of gentamicin resulted in undetectable levels in 93.94% of patients and < 0.001 mg/ml in 6.6% of patients.[30] None of the trials using gentamicin assessed hearing impairment. After 3 years of extensive use of gentamicin lock solutions, there was no emergence of resistance from the centers where one of the included RCTs was conducted.[34] Vancomycin at 25 mg/ml was reported to be undetectable in 90.1% of patients and < 0.0005 mg/ml in 9.9% of patients.[30] Manufacturers of ALS and/or the process of preparation by a pharmacist or nurse were reported in 9 trials.[10,12,14,15,29,31,33,35,36] One trial described detailed precautions taken to ensure stability of ALS during the study period. *In vitro* bactericidal efficacy of the ALS was also microbiologically evaluated in that trial.[10]

Most of the trials excluded participants with tunnel infection, exit site infection, localized/systemic infection, drug allergy, pregnant women and prolonged antibiotic usage. One trial excluded subjects with catheter blood flow rates < 300 ml/min.[35] Prophylactic use of antibiotics was employed in only one trial where a single dose of intravenous cephalothin was given to all the patients before catheter insertion.[8] In all the other trials patients were not on simultaneous systemic antibiotic therapy either for prophylaxis or treatment. In one of the trials, it was reported that one patient that was randomised to the heparin group developed endocarditis requiring valve replacement.[31]

Findings from meta-analysis

When all the 16 trials were included the REM pooled RR of CRBSI per patient was significantly lower with ALS compared with heparin alone lock solution (RR = 0.20; 95% CI = 0.13-0.31) (Figure 2). Heterogeneity was statistically significant (I^2=85.8%, $p < 0.0001$). No publication bias (Begg's test, $p = 0.064$; Egger's test, $p = 0.513$) (see Figures 3 and 4). Sensitivity analysis showed no trial unduly weighed on the estimate. The REM pooled RR of developing CRBSI among the ALS and heparin group was 0.10; 95% CI = 0.08-0.12 and 0.40; 95% CI = 0.30-0.51, respectively. Thus, the efficacy of ALS in preventing CRBSI was 80% with NNT of 3.3.

Restricted analysis

When 5 trials that used gentamicin in combination with citrate/heparin were combined the REM pooled RR (95% CI) of CRBSI was 0.06 (0.01-0.25). No publication bias (Begg's test, $p = 1.000$, Egger's test, $p = 0.034$).[8–10,28,34] The concentrations of gentamicin used in these trials were 40 mg/ml, 5 mg/ml, 4 mg/ml and 0.32 mg/ml as shown in Table 1. From 3 trials that used low dose gentamicin (0.32 mg/ml to 5 mg/ml) in combination with citrate/heparin the REM pooled RR (95% CI) of CRBSI was 0.03(0.01-0.13).[9,10,34] The FEM pooled RR (95% CI) of CRBSI from 2 trials that used high dose gentamicin (40 mg/ml) in combination with citrate was 0.18 (0.03-0.98).[8,28] Comparison of RRs derived from trials that used low dose and high dose gentamicin yielded RRR (95% CI) of 0.2 (0.02 - 1.61), $p = 0.126$.

From 2 trials that compared cefotaxime containing ALS with control the REM pooled RR (95% CI) of CRBSI was 0.38 (0.32-0.44).[12,36] Two trials also compared minocycline containing ALS with control and the REM pooled RR (95% CI) of CRBSI was 0.24 (0.10-0.56).[10,31] Another 2 trials compared gentamicin combined with either vancomycin or cefotaxime ALS with control and the REM pooled RR (95% CI) of CRBSI was 0.12 (0.05-0.29).[11,30] Non-antibiotic ALS (Taurolidine and/or Citrate) where compared with control in 3 trials and the FEM pooled RR (95% CI) of CRBSI was 0.44 (0.31-0.62).[14,15,29]

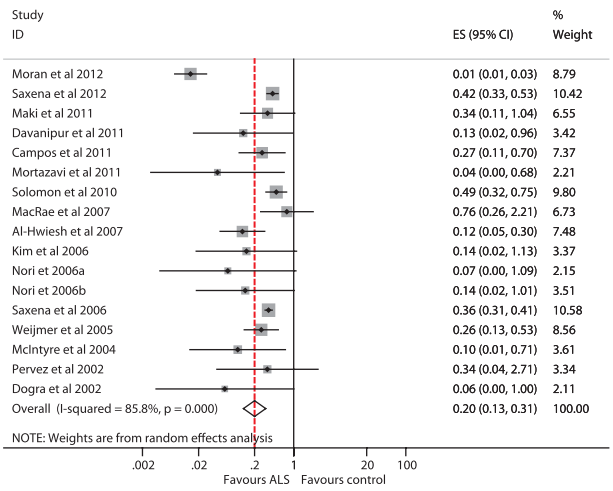

Figure 2: Forest plot showing RR of developing CRBSI among patients on chronic HD.

Table 1: Characteristics of studies included in the meta-analysis

Author	Sample size	Catheter days (ALS, controls)	Catheter type	Catheter care	CRBSI definition	ALS
Moran et al. (2012)[34]	303	39827, 32933	TCC	Triple antibiotic*	Non-CDC	GTC-0.32 mg/ml, CTR- 4%
Saxena et al. (2012)[36]	82	14965, 17155	TCC	Non	CDC	CFO-10 mg/ml
Maki et al. (2011)[33]	407	25266, 24390	Not clear	NA	Non-CDC	CTR-7.5%, MB, MP, PPP
Davanipur et al. (2011)[32]	100	1750, 1625	TCC	NA	NA	CLOX-100 mg/ml
Campos et al. (2011)[31]	187	4371, 4376	TCC/NTC	Chlorhexidine/ alcohol	CDC	MNC-3 mg/ml, EDTA-30 mg/ml
Mortazavi et al. (2011)[33]	30	NA	TCC	Antiseptic/topical mupirocin	CDC	CFO-10 mg/ml
Solomon et al. (2010)[15]	107	8129, 9642	TCC	Chlorhexidine/ alcohol	Non-CDC	TRD-1.35%, CTR- 4%
Al-Hwiesh et al. (2007)[30]	63	7212, 7656	TCC	Iodine solution	CDC	VCM-25 mg/ml, GTC-40 mg/ml
MacRae et al. (2008)[29]	61	92, 105	TC	NA	Non-CDC	CTR- 4%
Saxena et al. (2006)[12]	96	18615, 21170	TCC	Oxygen permeable dressing	CDC	CFO-10 mg/ml
Kim et al. (2006)[11]	120	1884, 1233	NTC	NA	Non-CDC	CFZ-10 mg/ml, GTC-5 mg/ml
Nori et al. (2006)[10]	61	4455, 1734	TCC	NA	CDC	a) GTC-4 mg/ml, CTR-3.13%, or b). MNC-3 mg/ml, EDTA-30 mg/ml
Weijmer et al. (2005)[14]	291	8431, 8116	TCC/NTC	NA	CDC	CTR-30%
McIntyre et al. (2004)[9]	50	3252, 2470	TCC	Oxygen permeable dressing	CDC	GTC-5 mg/ml
Pervez et al. (2002)[28]	36	1613, 1311	TCC	Iodine	Non-CDC	GTC-40 mg/ml, CTR-46.7%
Dogra et al. (2002)[8]	83	3280, 2643	TCC	Chlorhexidine/ iodine	CDC	GTC-40 mg/ml, CTR-3.13%

*Neomycin, bacitracin and polymyxin
ALS: Antimicrobial lock solution; CRBSI: Catheter related blood stream infection; CDC: Center for Disease Control and Prevention; CFZ: cefazolin; CFO: cefotaxime; CTR: citrate; CLOX: cloxacillin; EDTA: ethylene diamino acetic acid; GTC: gentamicin; MB: methylene blue; MP: methylparaben; MNC: minocycline; NA: not available; NTC: Non-tunneled cuffed catheter; PPP: propylparaben; TRD: taurolidine; TCC: tunneled cuffed catheter; VCM: vancomycin

Quality of clinical evidence

As shown in Table 3 the quality of clinical evidence was high for low dose gentamicin and moderate for high dose gentamicin, cefotaxime, minocycline and taurolidine/citrate.

Meta-regression

Metaregression analysis involving all the 16 studies that reported catheter days showed no association between rate of CRBSI and catheter days. However, when the two studies[28,29] with < 3000 catheter days were excluded meta-regression analysis showed significant association between rate of CRBSI and catheter days (slope curve coefficient = 2.35, p = 0.037, 95% CI = -1.1406 to + 0.0001) (see Figure 5). Rate of CRBSI rises with increasing proportion of diabetic patients though did not reach statistical significance (slope curve coefficient = 1.79, p = 0.099, 95% CI = -0.001 to + 0.01). There was a trend towards decreasing rate of CRBSI with increasing PCV though not statistically significant (slope curve coefficient = -0.53, p = 0.610, 95% CI = -0.001 to + 0.0063).

Discussion

This systematic review and meta-analysis of 16 RCTs involved 2016 adults with 279 701 catheter days. The treatment and the control groups had similar demographic and laboratory characteristics. The two different statistical tests used did not detect publication bias and, where heterogeneity was encountered between studies, estimates were derived using REM.

The risk of CRBSI was significantly lower in ALS group as compared to heparin only lock group with an efficacy of 80%. The risk of CRBSI in the heparin only lock group was 4 times that of the ALS group translating into NNT of 3 patients to prevent one CRBSI. All the RCTs included in the meta-analysis compared ALS with heparin and none conducted a head-to-head comparison of antibiotics. Hence, it is difficult to determine the most effective ALS in preventing CRBSI. Precipitation of antibiotics in heparin solution was not reported among all the seven trials that used antibiotics in heparin.[9,11,12,30,32,35,36] It is believed that precipitation is concentration dependent and more likely to occur with high concentration of antibiotics in low concentration of heparin.[37] With the exception of one trial,[9] all the other trials have applied this principle because those trials using high[12,30,35,36] concentration of antibiotics used high concentration of heparin (5000 IU/ml) while those using low[11,32] concentrations of antibiotics have used low concentration of

Table 2: Assessment of study quality using the GRADE approach

Characteristics of included studies		GRADE Factors									
Author	ES	RCT design	Large effect size	Study limitations	Inconsistency	Indirectness	Imprecision	Exposure-response gradient	Plausible confounding	Publication bias	Overall quality
Moran (2012)[34]	2.54	✓	✓	✓	✓	✓	✓	NA	✓	✓	++++
Saxena (2012)[36]	0.48	✓	X	✓	✓	X	X	NA	✓	✓	++
Maki (2011)[33]	0.59	✓	X	✓	✓	✓	X	NA	✓	✓	+++
Davanipur (2011)[32]	1.13	✓	✓	✓	✓	X	✓	NA	X	✓	+++
Campos (2011)[31]	0.72	✓	X	X	✓	✓	✓	NA	✓	✓	+++
Mortazavi (2011)[35]	1.78	✓	✓	X	✓	✓	X	NA	✓	✓	+++
Solomon (2010)[15]	0.39	✓	X	X	✓	✓	✓	NA	✓	✓	+++
Al-Hwiesh (2007)[30]	1.17	✓	✓	✓	✓	X	X	NA	✓	✓	+++
MacRae (2008)[29]	0.15	✓	X	✓	✓	X	X	NA	✓	✓	++
Saxena (2006)[12]	0.56	✓	X	✓	✓	X	X	NA	✓	✓	++
Kim (2006)[11]	1.09	✓	✓	X	✓	X	X	NA	✓	✓	++
Nori (2006)[10]	1.47	✓	✓	✓	✓	✓	X	NA	✓	✓	+++
Nori (2006)[11]	1.09	✓	✓	✓	✓	✓	X	NA	✓	✓	+++
Weijmer (2005)[14]	0.74	✓	X	✓	✓	✓	✓	NA	✓	✓	++++
McIntyre (2004)[9]	1.27	✓	✓	✓	✓	X	X	NA	✓	✓	+++
Pervez (2002)[28]	0.59	✓	X	✓	✓	X	X	NA	✓	✓	++
Dogra (2002)[8]	1.55	✓	✓	✓	✓	✓	X	NA	✓	✓	+++

✓– No serious limitation, inconsistency, indirectness, imprecision, publication bias, plausible confounding (or presence of large effect size and exposure-response gradient)
X – Presence of serious limitation, inconsistency, indirectness, imprecision, publication bias, plausible confounding (or absence of large effect size and exposure-response gradient)
Overall quality of evidence: + - very low; ++ - low; +++ - moderate; ++++ - high
RR: relative risk; CI: confidence interval; GRADE: Grading of Recommendations Assessment Development and Evaluation; NA: not available; ES: effect size

heparin (1000 IU/ml). The trial that used low concentration of gentamicin (5 mg/ml) in high concentration of heparin (50000 IU/ml) reported no systemic heparinisation.[9]

Gentamicin was the most common antibiotic used in the trials and showed significant benefit in reducing CRBSI. Low dose gentamicin lock solution appeared to show similar benefit in preventing CRBSI compared to high dose gentamicin lock solution. In addition, low dose gentamicin is associated with a lesser risk of toxicity from systemic leakage and subsequent development of drug resistance. One of the included RCTs that used low dose gentamicin (0.32 mg/ml) reported no emergence of resistance to gentamicin from their center from 2008 to 2012, despite routine usage as a catheter locking agent.[34] A 7-year longitudinal study involving chronic HD patients used 5 mg/ml gentamicin in 1% Heparin with a mean (range) trough level of 170 (50-310) mg/ml among the cohort. They reported no resistance to gentamicin and no ototoxicity after 7 years of follow-up.[38] In contrast, use of high dose gentamicin (40 mg/ml) as a catheter lock is associated with systemic exposure to gentamicin in one of the included RCTs, and could potentially predispose patients to drug toxicity and development of drug resistant microorganisms.[8] Only one study so far reported gentamicin-resistant microorganisms in HD patients using gentamicin as a catheter locking agent to prevent CRBSI.[39] However, the reliability of this finding is limited by the uncontrolled retrospective design of the study. Vancomycin-resistant *Staphylococcus aureus* (VRSA)[40] has also been documented; and this is a major concern as both gentamicin and vancomycin are routinely used in the treatment of CRBSI.[31] Minocycline is not routinely used in management of CRBSI and has been found to be very potent in eradicating microorganisms inside biofilm,[41] while cefotaxime has a good safety profile in HD and severely ill patients.[42,43] Cardiotoxicity and catheter blockage are associated with trisodium citrate and taurolidine citrate

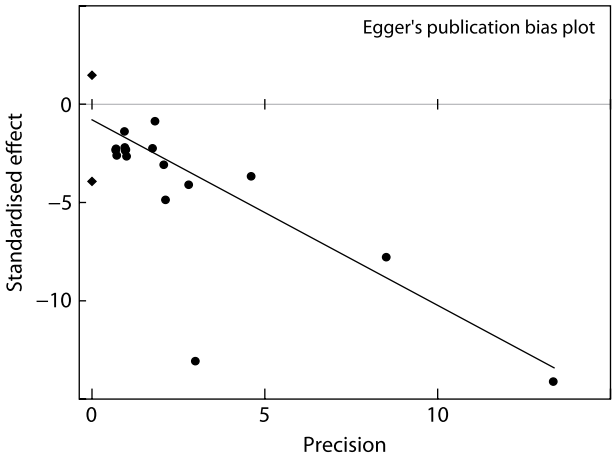

Figure 3: Egger's plot assessing small study effect.

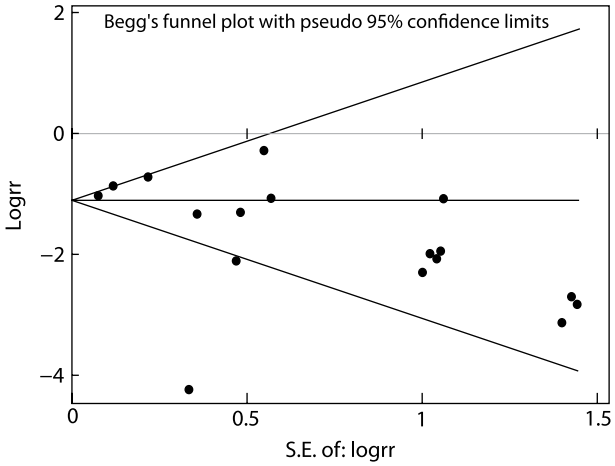

Figure 4: Begg's Funnel plot assessing publication bias.

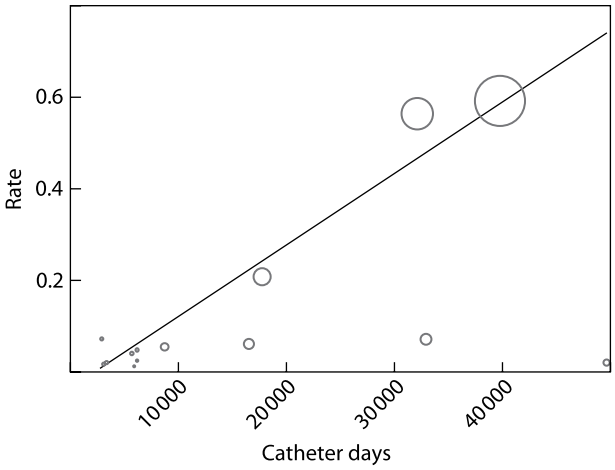

Figure 5: Meta-regression of RR of developing CRBSI by catheter days. Slope curve coefficient = 2.35, $p = 0.037$, 95% CI = -1.1406 to + 0.0001.

when used as catheter lock solutions.[36] There has been concern about the efficacy and safety of citrate at varying concentrations. Adverse effects are common at higher concentrations of citrate,[44] while low concentrations were found to be ineffective in preventing CRBSI.[45]

A major challenge with diagnosis of CRBSI in routine clinical practice is that signs of inflammation at the catheter insertion site may not accurately predict CRBSI.[46] Majority of the included studies used CDC criteria to define CRBSI. Although this criterion has high sensitivity, its poor specificity for CRBSI is a major concern.[47] All the included RCTs reported *Staphylococcus aureus* among ALS and heparin groups causing CRBSI. End-stage renal disease (ESRD) patients receiving HD are at increased risk of developing *Staphylococcus aureus* septicemia,[48,49] a condition associated with a longer stay in hospital with a high cost of treatment.[50] Endocarditis requiring valve replacement occurred in a patient on the heparin lock solution in one of the trials. In that trial the most common bacteria cultured from blood in the heparin lock group were *Staphylococcus aureus*, coagulase negative Staphylococcus, *E. coli* and *Enterobacter aerogenes*, in that order.[31] The mortality rate has been reported to be higher among patients hospitalised with *Staphylococcus aureus* bacteremia as compared to those with *Staphylococcus aureus* non-blood stream infection.[50] Apart from infective endocarditis, other life-threatening complications that could occur in the setting of *Staphylococcus aureus* septicemia include meningitis and metastatic abscesses.[51,52] Use of topical or intranasal mupirocin[8,14,35] and triple antibiotic ointment[34] for catheter care in some of the trials in this meta-analysis could affect the type of microorganism cultured in patients with CRBSI. Bacterial biofilm usually originates from the normal bacterial flora on the skin at the exit-site of the catheter.[53] In the trial by Dogra et al., nasal mupirocin was given for prophylaxis against CRBSI. This could have lead to the predominance of gram-negative CRBSI over *Staphylococcus aureus* CRBSI as explained by the authors.[8]

Cost and availability are important factors in healthcare intervention which could influence the process of decision making. Among the trials included in this review only three recognise the cost of ALS.[10,11,14] Citrate is more expensive than heparin but readily available, whereas taurolidine is also expensive but not readily available. The monthly cost of gentamicin/citrate lock solution per-patient is 4 times that of minocycline/ethylene diamino acetic acid lock solution.[10] Complete treatment of an episode of CRBSI could cost up to US$25 000 to US$45 000.[54] In addition, CRBSI increases cost of hospitalisation and duration of hospital stay.[53] Hours of productivity lost during admission for CRBSI together with drug and non-drug costs associated with CRBSI adds to the financial burden imposed by ESRD. Prophylactic ALS could reduce this financial burden of CRBSI incurred by patients. A conservative analysis estimated that a 50% reduction in episodes of CRBSI from prophylactic ALS could save patients up to US $5,000 per annum.[55] However, this cost benefit could easily be abolished by development of drug-resistant microorganisms that require prolonged hospital stays and expensive antibiotics.[56]

Accuracy of ESs derived in this meta-analysis could be limited by some methodological factors in the trials. Predictive value measures such as sensitivity and specificity of the non-CDC definition of CRBSI used in some of the RCTs may not be as good as that of CDC definition. Proper assessment of drug toxicity and development of drug-resistant microorganisms was not possible due to the short duration of the follow-up period in some of the trials. Only one trial reported precautions taken to ensure stability of the ALS during the study period.[10] Further, *in vitro* stability of antibiotics in heparin lock solutions was not tested in all seven trials which used antibiotics in heparin solution.[9,11,12,30,32,35,36] However, this is unlikely to affect results of the meta-analysis because none of these studies reported precipitation of antibiotics in heparin solution. Strength of this meta-analysis includes a large sample size and number of

Table 3: Assessment of quality of clinical evidence and strength of recommendation using the GRADE approach

		Outcome assessed-efficacy of ALS in preventing CRBSI among HD patients					
		All ALS	High dose Gentamicin	Low dose Gentamicin	Cefotaxime	Minocycline	Taurolidine/ Citrate
Baseline parameters	Number of studies	Sixteen	Two[8,28]	Three[9,10,34]	Two[12,36]	Two[10,31]	Three[14,15,29]
	Total sample size	2016	119	414	178	248	459
	Total catheter days	279 701	8 847	84 671	71 905	14 936	126 423
GRADE factors	RCT design	✓	✓	✓	✓	✓	✓
	Plausible confounding	✓	✓	✓	✓	✓	✓
	Study limitations	✓	✓	✓	✓	✓	X
	Inconsistency	X	✓	✓	✓	✓	✓
	Indirectness	✓	✓	✓	✓	✓	✓
	Imprecision	✓	X	✓	✓	✓	✓
	Publication bias	✓	✓	✓	✓	✓	✓
	Large effect size	✓	✓	✓	X	X	X
	Exposure-response gradient	X	X	X	X	X	✓
	Overall quality	+++	+++	++++	+++	+++	+++

✓– No serious limitation, inconsistency, indirectness, imprecision, publication bias, plausible confounding (or presence of large effect size and exposure-response gradient)
X – Presence of serious limitation, inconsistency, indirectness, imprecision, publication bias, plausible confounding (or absence of large effect size and exposure-response gradient)
Overall quality of evidence: + - very low; ++ - low; +++ - moderate; ++++ - high
ALS: Antimicrobial lock solution; CRBSI: Catheter-related blood stream infection; GRADE: Grading of Recommendations Assessment Development and Evaluation; HD: Haemodialysis

catheter days. In comparison to previously conducted meta-analyses,[57,58] this study included recently published articles and this allowed for restricted analysis with respect to low and high dose gentamicin. Moreover, application of the GRADE system of assessing quality of studies provided opportunity for rating strength of clinical recommendations.

In conclusion, ALS are effective in preventing CRBSI although drug toxicity is a major concern. Low dose gentamicin should be preferred to high dose gentamicin as it offers similar benefit in preventing CRBSI with lesser risk of toxicity from systemic leakage and subsequent development of drug resistance. Further studies are needed for a head-to-head comparison of antimicrobial agents in order to provide guidelines for clinical practice.

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